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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,355	01/31/2005	Robert J. Hariri	9516-149-999	2178

20583 7590 12/06/2005

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 12/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,355	HARIRI ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-101* is/are pending in the application.

4a) Of the above claim(s) *5,12,17-24,28 and 34-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,13-16,25-27 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/27/05, 2/17/05, 3/25/05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment received 10/6/05 amending claims 1-6, 8, 9, 11-30, 32-34, 36-53, 56-59, 71, 74, 75, 77-79, 81, 83-90, 95-98, 100, and 101 and canceling claim 10 is acknowledged. Claims 1-9 and 11-101 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-8, 25-33, and 46-49, in the reply filed on 10/6/05 is acknowledged. The traversal is on the ground(s) that the Groups are unified by a special technical feature and that claims 9-16 have been amended such that they depend directly from the claims of Group I. This is found persuasive in part because the amendments to claims 9 and 11-16 necessitate rejoinder of these claims to Group I. Groups III-XII remain restricted.

Applicant's arguments have been carefully considered, but the fact remains that the unifying feature of the inventive Groups is merely the treatment of stem cells with a phosphodiesterase IV (PDE4) inhibitor, which does not qualify as a **special** technical feature. The expression "special technical feature" refers to those features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. Thus, a feature found in the prior art cannot be considered to be a special technical feature. See PCT Rule 13.2. In this case, the treatment of cells with PDE4 inhibitors is well known in the art. WO 01/93909 (2001; reference B37 on 2/17/05 IDS), for example, teaches treating (Example 2) bone marrow (which comprises numerous types of stem cells; see page 37, lines 9-11) with rolipram (Figure 11c, page 92), which is a small-molecule PDE4 inhibitor that is not a polypeptide, hormone, cytokine, or

nucleic acid. The treatment method of WO '909 results in cells whose differentiation and growth patterns are modulated (Examples 3-8, especially Examples 4 and 8).

Groups III, VII, and VIII are drawn to treatment methods of an entire mammalian subject and therefore do not share the technical feature of Group I (*i.e.*, contacting stem cells directly with a PDE4 inhibitor), since the effect of the methods of Groups III, VII, and VIII may be via indirect means not involving interaction of PDE4 inhibitors with stem cells. Groups IV-VI and X are drawn to compositions comprising cells which may be made by specific processes, but product-by-process limitations are considered only to the extent that the process affects the claimed product. In this case, the claims have been interpreted as being drawn simply to populations of cells that may be made by any number of methods. The methods of Groups IX and XI are drawn to contacting cells with PDE4 inhibitors, but the scope of these claims is broader than that of Group I, which limits the type of PDE4 inhibitor to be employed. The examiner declines to rejoin Groups III-XI to new Group I or to each other.

The examiner also points out that the scope of claims 1-8 and 25-33 was narrowed by amendment (*i.e.*, the PDE4 inhibitor may not be a polypeptide, hormone, cytokine, or nucleic acid), but the scope of claims 46-49 was not similarly narrowed. As such, claims 46-49 are restricted from Group I into new Group XII and will be withdrawn as being drawn to a nonelected invention.

The restriction requirement is still deemed proper and is therefore made FINAL. Claims 17-24, 34-49, and 50-101 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Applicant timely traversed the restriction requirement in the above reply.

Applicant's election with traverse of various species in the same reply is acknowledged. The traversal is on the ground(s) that no undue burden would be placed on the examiner in considering each and every claimed embodiment. This is not found persuasive because burden is not a consideration in the restriction requirements for cases filed under 35 U.S.C. § 371. The requirement is still deemed proper and is therefore made FINAL.

Claims 5, 12, and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the election requirement in the above reply.

The examiner notes for the record that applicant has failed to comply with the requirement to elect ONE end point of differentiation (see page 3 of restriction requirement); however, in the interest of compact prosecution, the requirement for this species election ONLY is withdrawn. The examiner also notes applicant's amendment of claim 4 in which "SelCID" was replaced with "selective cytokine inhibitory drug"; in light of this amendment, applicant's election of "selective cytokine inhibitory drug" as a PDE4 inhibitor is acceptable.

Examination will commence at this point on claims 1-9, 11, 13-16, 25-27, and 29-33 ONLY, to the extent they read on the elected species (placental stem cells; selective cytokine inhibitory drug; differentiation within an individual; and CD34+ progenitor cell).

Information Disclosure Statement

The information disclosure statements received 1/27/05, 2/17/05, and 3/25/05 have been considered by the examiner. The examiner wishes to clarify that references A01-A07 will not be considered or printed on the face of the patent, because U.S. provisional applications are not a matter of public record. Reference A08 lists the serial number of a pending case, which should be replaced with the published application number (in this case, 2005/0148034). References B14, B18, and B19 were provided in their entirety, but translations were provided only for the abstracts of these German-language documents. References B34-B36 were provided in their entirety, but no translations of any kind were provided for these German-language documents.

Specification

The incorporation of essential material in the specification by reference to an **unpublished U.S. application, foreign application or patent, or to a publication** is improper. For example, at page 1, lines 5-6, applicant improperly incorporates by reference numerous unpublished U.S. provisional applications; at page 44, line 18, applicant improperly incorporates by reference numerous foreign patent documents; at page 45, line 11, applicant improperly incorporates by reference numerous non-patent publications. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The use of various trademarks, including "SelCID", "MATRIGEL", "displayPROFILE", "PCR-Select", and "Mesen Cult", has been noted in this application (for example, at page 6, line 19; page 15, line 14; page 21, line 29; page 21, line 32; and page 22, line 10, respectively). These and all trademarks should be capitalized wherever they appear **and** be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

Claims 1-9, 11, 13-16, 25-27, and 29-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of modulating some aspects of proliferation and differentiation of mammalian stem or progenitor cells to varying degrees using a few PDE4 inhibitors, does not reasonably provide enablement for methods of inducing specific differentiation end points (including the production of hematopoietic cells) comprising treating any given mammalian stem or progenitor cell with any given PDE4 inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention

based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Directing the differentiation or proliferation of stem cells to a particular end is a major problem in the stem cell art, despite the relatively high level of ordinary skill therein. At the time of the invention, numerous types of stem cells were known in the art. For example, Pittenger et al. (1999, *Science* 284: 143-147; reference U) teach a population of non-hematopoietic mesenchymal stem cells (MSCs) isolated from bone marrow (Abstract) that was known in the early 1980s (references 3-5). As a further example, Rossant (2001, *Stem Cells* 19:477-482; reference V) teach embryonic stem (ES) cells, which are isolated from the ICM of blastocysts. Even after the time of the invention, differentiating these or any particular stem cell or precursor cell to a particular end point remains a major problem in the art. For example, Gregory et al. (2005; *Experimental Cell Research* 306: 330-335; reference W) teach that even years after the time of the invention, the MSCs of Pittenger et al. are still being evaluated for their degree of pluripotency (page 333); Glaser et al. (2005, *Trends in Neuroscience* 28: 397-400; reference X) teach that the ES cells of Rossant are easily differentiated to neuronal precursors, but differentiation to neurons or glia *per se* has proven impossible so far (Abstract; Figure 2). In light of the unpredictable nature of the stem cell differentiation art and the breadth of the claims, the specification fails to provide sufficient guidance for every claimed embodiment.

Even if the claims are narrowly construed as being drawn to directing differentiation to hematopoietic cell, the specification still fails to be enabling for the

claimed invention. Gregory et al. teach that bone marrow MSCs can be differentiated into myoblasts, hepatocytes, and possibly neural cell types, but not hematopoietic cells (page 332). Specifically, Pittenger et al. teach methods for differentiating MSCs into adipogenic, chondrogenic, and osteogenic lineages (Figure 2). The specification and art provide no guidance for differentiating these MSCs into hematopoietic cells.

Even if the claims are narrowly construed as being drawn to methods of modulating the differentiation or proliferation of placental stem cells, the specification still fails to be enabling for the claimed invention. According to the above-cited 2001 review by Rossant, trophoblast stem (TS) cells, which arise from the trophectoderm (non-ICM) of the developing embryo, give rise to cells of the trophoblast lineage (*i.e.*, placenta) but no other cell types (page 479, column 2, paragraph 4). Hematopoietic stem cells (HSCs) were discovered in the placenta after the instant invention was made; Mikkola et al. (2005, *Experimental Hematology* 33: 1048-1054; reference U2) review methods by which placental HSCs may be isolated, but said methods were not published until 2005 (page 1049, column 2, through page 1050, column 1; references 15 and 16 in Mikkola et al.). The specification provides insufficient guidance such that the person of ordinary skill in the art would have a reasonable expectation of success in treating TS cells with any PDE4 inhibitor and obtaining any given effect on differentiation or proliferation. Indeed, the specification provides insufficient guidance for such treatment of placental HSCs, because said cells were unknown at the time of the invention.

Finally, applicants present only prophetic working embodiments speculating as to the effect of treating CD34+ cells with PDE4 inhibitors. No experimental data is presented, and no evidence that the experiments of Examples 1-14 were actually conducted is provided. While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

Claims 1-9, 11, 13-16, 25-27, and 29-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

M.P.E.P. § 2163 recites, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention... one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

The claims are broadly drawn to methods comprising contacting mammalian stem or progenitor cells with a compound that inhibits PDE4 activity but is not a polypeptide, hormone, cytokine, or nucleic acid; in some dependent claims, these compounds are further described as being "selective cytokine inhibitory drugs." The specification gives numerous examples of PDE4 inhibitors that are not polypeptides, hormones, cytokines, or nucleic acids (pages 25-44) but provides no guidance by which other PDE4 inhibitors might be identified.

The specification provides no structural information about the selective cytokine inhibitory drugs of claims 4 and 27. These drugs (the so-called "SelCIDs") are described as being produced by the Celgene Corporation; a cursory search of the scientific literature revealed that these drugs are thalidomide derivatives, but failed to produce any structural data. The specification describes the "preferred" SelCIDs in terms of their function (inhibition of TNF-a production; mild inhibition of lipopolysaccharide-induced interleukin production; page 25, lines 33-35), but provides no guidance as to identifying a particular drug as a SelCID or, indeed, to determining whether said drug is appropriate for use in the claimed method.

M.P.E.P. §2163 recites, "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient

to show the applicant was in possession of the claimed genus...when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. **For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.**"

The PDE4 inhibitors discussed in the specification are diverse in structure, ranging from substituted cyclic amides to substituted alkanohydroxamic acids to substituted phenethylsulfones to substituted isoindolyl compounds. The family of PDE4 inhibitors, therefore, is not characterized by any specific structural criteria that would cause the person of ordinary skill in the art to envisage immediately all PDE4 inhibitors given only the information in the specification and that encompassed in the prior art.

The claims are currently in means-plus-function form (*i.e.*, compounds that inhibit PDE4 activity); M.P.E.P. §2163 teaches that such claims are adequately described if "the written description adequately links or associates adequately described particular structure, material, or acts to the function recited in a means-plus-function claim limitation", or if "it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a means-plus-function limitation". The instant disclosure does not meet either of these criteria. As detailed above, the specification does not link any specific compound to the claimed activity, and because of the diversity of the genus of PDE4 inhibitors, the skilled artisan would not be able to determine which compounds do or do not perform the

claimed function (inhibition of PDE4 activity) without extensive experimentation. See 35 U.S.C. §112, sixth paragraph.

Claims 1-9, 11, 13-16, 27, and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing in that it is drawn to a method for "modulating the proliferation or differentiation of a [cell]" but requires said cell to be contacted with a PDE4 inhibitor until such time as "differentiation of the [cell] has been modulated." It is not clear how the steps of the method, which only recite modulating differentiation, can result in one of the effects claimed in the preamble, *i.e.* an effect on proliferation. Clarification is required.

Claim 1 is further confusing in that it requires that the claimed contacting occur "under suitable conditions" without particularly defining the same. It is not clear whether the conditions must be suitable for the contacting itself; for modulating the proliferation of a cell; for modulating the differentiation of a cell; for the inhibition of PDE4 activity; for a combination of these; or for some other event altogether. Clarification is required.

Because claims 2-9, 11, and 13-16 depend from indefinite claim 1 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 2 is confusing because it is not clear whether the limitation "wherein said cell differentiates into a hematopoietic cell" recites an inherent effect of the steps of

claim 1 or recites additional method steps. If the latter is the case, the claim should be amended to recite particular steps yielding the claimed result. Clarification is required.

Claim 2 is further confusing in that it depends from claim 1, which is drawn in part to a method of modulating proliferation of a cell, but requires said cell to differentiate. Proliferation and differentiation are processes having opposite effects. It is not clear whether claim 2 is compatible with amended claim 1. Clarification is required.

Claim 3 is confusing in that it includes as species "embryonic stem cells", "placental stem cells", and "cord blood stem cells." It is not clear to what extent, if any, these terms overlap. Placental stem cells, as defined by the specification, are "not derived from the inner cell mass (ICM) of a blastocyst" (page 11, lines 11-19), but this definition still includes various cells that may be isolated from the trophectoderm, which is one part of the embryo. Therefore, the term "embryonic stem cell" encompasses "placental stem cell". Similarly, the umbilical cord can be considered to be one component of the placenta. As such, the term "placental stem cell" encompasses "cord blood stem cell", and both of these are types of "embryonic stem cell." Clarification is required. In the interest of compact prosecution, the examiner has interpreted the elected species "placental stem cell" as being a stem cell that is isolated from the placenta in any manner; therefore, the definition encompasses ES cells and cord blood stem cells.

Claim 4 is confusing in that it recites the term "selective cytokine inhibitory drug" without particularly defining the same. Selective cytokine inhibitory drugs are discussed, for example, at page 25 of the specification. They are described as being products of

the Celgene Corporation and are further described in terms of a few of their functions, but no chemical structure is suggested or implied for the same. It is not clear which small molecules are encompassed and which are excluded by this claim term. Clarification is required.

Claim 6 requires that the contacting of claim 1 be conducted "within a subject", which is confusing. The claim does not point out any relationship between the subject of claim 6 and the cell and molecules of claim 1. In addition, the term "subject" does not necessarily further limit claim 1, since a culture dish could be considered a "subject." The specification provides no insight into the identity of said subject. Clarification is required.

Claim 9 is confusing in that it requires the cell of claim 1 to be "a CD34+ progenitor cell." It is not clear whether this phrase describes some progenitor cell that is itself CD34+, or some cell that gives rise to cells that are themselves CD34+, or to some other population. Clarification is required.

Claim 11 is confusing because it is not clear whether the limitation "wherein said cell differentiates into a CD34+ CD38- CD33+ or CD34+ CD38- CD33- cell" recites an inherent effect of the steps of claim 1 or recites additional method steps. If the latter is the case, the claim should be amended to recite particular steps yielding the claimed result. Clarification is required.

Claim 13 requires that the contacting of claim 9 be conducted "within a subject", which is confusing. The claim does not point out any relationship between the subject of claim 13 and the cell and molecules of claim 9. In addition, the term "subject" does not

necessarily further limit claim 9, since a culture dish could be considered a "subject." The specification provides no insight into the identity of said subject. Clarification is required.

Claim 14 requires that the contacting of claim 9 be conducted "within a subject", which is confusing. The claim does not point out any relationship between the subject of claim 14 and the cell and molecules of claim 9. In addition, the term "subject" does not necessarily further limit claim 9, since a culture dish could be considered a "subject." The specification provides no insight into the identity of said subject. Clarification is required.

Claim 14 is further confusing in that it is not clear whether the transplanting step therein occurs before or after the contacting step of claims 9 and 13. Clarification is required.

Claim 15 is confusing in that it references a measurement "relative to a control" but does not particularly characterize said "control." Clarification is required.

Claim 27 is confusing in that it recites the term "selective cytokine inhibitory drug" without particularly defining the same. Selective cytokine inhibitory drugs are discussed, for example, at page 25 of the specification. They are described as being products of the Celgene Corporation and are further described in terms of a few of their functions, but no chemical structure is suggested or implied for the same. It is not clear which small molecules are encompassed and which are excluded by this claim term. Clarification is required.

Claim 31 is confusing in that it requires that "the differentiation" of claim 25 "is differentiation into a hematopoietic cell." Claim 25 does not necessarily require differentiation of cells; it is also drawn to a method of modulating the proliferation of cells. Because claims 32 and 33 depend from indefinite claim 31 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6-8, 25, 29, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Pittenger (1998, U.S. Patent 5,827,740; reference A). The claims are drawn to a method for modulating the proliferation or differentiation of a mammalian stem cell comprising contacting said cell with a compound that inhibits PDE4 activity and is not a polypeptide, hormone, cytokine, or nucleic acid; and a composition that may be made thereby. In some dependent claims, the contacting is conducted within a subject; in some dependent claims, the compound is present in a particular concentration; in some dependent claims, the cell is human.

Pittenger teaches a method for differentiating human mesenchymal stem cells (MSCs) into adipocytes comprising contacting said cells with methyl isobutylxanthine (Example 1; column 8, lines 11-17). Pittenger teaches that methyl isobutylxanthine is a general phosphodiesterase inhibitor (column 5, lines 6-9). The cell culture dish of Pittenger is a "subject" according to the broadest reasonable definition of the term (*i.e.*, "that which experiences or is subjected to a treatment").

Claims 1, 2, 6, 7, 9, 11, 13-15, 25, 29, and 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Gaspar Elsas et al. (2000, *British Journal of Pharmacology* 130: 1362-1368; reference W2). The claims are drawn to methods and compositions as above. In some dependent claims, the stem cells are CD34+ precursor cells. In some dependent claims, the differentiation to be modulated is differentiation to a hematopoietic cell.

Gaspar Elsas et al. teach treating mouse bone marrow, which comprises CD34+ hematopoietic stem cells (HSCs) with rolipram, a PDE4 inhibitor (page 1363, column 2, paragraph 2; table 1). Treating the cells of Gaspar Elsas et al. with rolipram affects the degree of colony formation by said cells (Table 1), which is an indicator of differentiation. The cell culture dish of Gaspar Elsas et al. is a "subject" according to the broadest reasonable definition of the term (*i.e.*, "that which experiences or is subjected to a treatment"). Claim 11 is included in this rejection because the differentiation to cells expressing the claimed combination of markers is an inherent property of CD34+ cells.

Claims 1, 2, 6-9, 11, 13-15, 25, and 29-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Davis et al. (2003, U.S. Patent Application Publication

2003/0171306; reference B). The claims are drawn to methods and compositions as above. In some dependent claims, the cells are human.

Davis et al. teach isolating CD34+ stem cells from human bone marrow and treating said CD34+ cells with rolipram (Example 2; paragraph 0177), a PDE4 inhibitor (paragraph 0069). Davis et al. teach that said treatment reduces apoptosis in CD34+ cells also treated with paclitaxel (paragraph 0178); therefore, the proliferation of the cells is modulated. Davis et al. further teach that treating CD34+ cells with rolipram protects neutrophil progenitors from the toxic effects of paclitaxel (paragraph 0188), thus modulating the differentiation of the stem cells. Finally, Davis et al. teach that neutrophil progenitors treated with any of several PDE4 inhibitors are protected from the toxic effects of paclitaxel (Example 5; paragraph 0189). The cell culture dish of Davis et al. is a "subject" according to the broadest reasonable definition of the term (*i.e.*, "that which experiences or is subjected to a treatment"). Claim 11 is included in this rejection because the differentiation to cells expressing the claimed combination of markers is an inherent property of CD34+ cells.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 7-9, 11, 15, 16, 25, 26, and 29-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7, 9-11, 13, 20, 21, 30, 31, and 34-38 of copending, currently commonly assigned Application No. 10/411655, which shares three inventors in common with the instant application, in view of Feldman et al. (1997, U.S. Patent 5,665,754; reference C). Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the '655 application overlaps with some embodiments of the instant application.

The cited claims in the '655 application are identical to the cited claims in the instant application except for the fact that the methods and compositions of the '655 application involve TNF-α inhibitors, while those of the instant application involve PDE4 inhibitors. Feldman et al. is cited as evidence that PDE4 inhibitors, including rolipram, also inhibit the production of TNF-α (column 1, lines 54-64); at least some PDE4 inhibitors are, therefore, also TNF-α inhibitors. The scope of the cited claims in the '655 application and the instant application overlap to at least some extent, and possibly completely so.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lora E Barnhart

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SANDRA E. SAUCIER
PRIMARY EXAMINER